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Title: PHARMACOKINETICS OF ORALLY ADMINISTERED DESMOPRESSIN (DDAVP) IN HEALTHY YOUNG AND ELDERLY SUBJECTS AND IN THE NOCTURIA POPULATION.

Aims of Study:

Orally administered desmopressin has been available for the treatment of nocturnal enuresis and diabetes insipidus for more than 10 years. The data presented are collated from several studies taken from an extensive research program to describe the pharmacokinetics of oral desmopressin with respect to age, gender, time of administration (day or night), metabolism and food interaction in healthy and nocturic individuals.

Methods: Either 200 μg or 400 μg of desmopressin acetate (dDAVP) were administered orally to healthy or nocturic males or females with ages in the range of 18–85 years.

Results:

Data were obtained from 117 healthy individuals and 24 nocturic patients. The absolute bioavailability of oral desmopressin was highly variable and ranged from 0.08% to 0.16%, for desmopressin doses of 200 μg and 400 μg. The mean maximum plasma concentrations (C_{max}) in 75 healthy men (aged 18–75 years) were found to be in the range of 6.57–16.6 pg/ml for a 200 μg dose, and 31.4–51.6 pg/ml for a 400 μg dose of desmopressin, and were reached within 2 hours (T_{max} 0.75–1.9 h). Intra- and inter-individual variability in the absorption of desmopressin was great with coefficients of variation of more than 30% in 24 healthy young subjects (12 male and 12 female: aged 20–31 years). Preliminary studies have reported a significant gender related difference in pharmacokinetic parameters, however, these differences pointed in opposite clinical directions. Nevertheless, gender- and age-related differences were not supported in a subsequent pooled data analysis of several clinical studies. In a few patients, antidiuresis was registered despite undetectable plasma levels of desmopressin.

No differences in plasma desmopressin concentration were recorded when desmopressin was taken during the day or night (n=15, healthy male subjects aged 55–75 years). *In vitro* human liver microsome metabolism of desmopressin was found to be not significant and the terminal half-life was estimated to be 2.0–3.21 h using non-compartmental methods.

Conclusions:

There were no significant differences in the pharmacokinetics of desmopressin in nocturic and healthy subjects. Intake of desmopressin in the morning and evening had no effect on the circadian variation in plasma desmopressin concentration indicating that desmopressin has equal pharmacokinetic properties during the day and night. Furthermore, a pooled data analysis did not reveal any significant correlation between age or gender and desmopressin pharmacokinetics.

Extensive metabolism of desmopressin by the liver is unlikely, and previous data have estimated that 65% of the absorbed amount of desmopressin after oral dose is recovered unchanged in the urine (1). The renal clearance of dDAVP in healthy volunteers and renally impaired patients is currently being investigated.
The consequences of the variability in the absorption of desmopressin is unlikely to be of high importance as the plasma concentrations of desmopressin achieved in each study were in excess of the levels required for maximal antidiuretic effect. Nevertheless, the clinical impact of absorption needs to be investigated further as increased doses of desmopressin and hence increased plasma concentrations, results in prolonged duration of pharmacological action. Interestingly, increased doses do not necessarily produce a more pronounced antidiuretic effect as measured by urine production and osmolality changes and vice versa.

(1) Fjellestad-Paulsen A, Höglund P, Lundin S and Paulsen O. Pharmacokinetics of 1-deamino-8-D-arginine vasopressin after various routes of administration in healthy volunteers. Clin Endocrinol 38: 2, 177–182.

Source of funding:

Ferring Pharmaceuticals and Aventis.